PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF:	EXAMINER: **Thomas Sweeney Heard**
Michael David Bentley, et al.	ART UNIT: **1654**
APPLICATION NO.: **10/647,561**	CONF. NO: **3230**
FILED: **August 25, 2003**	
FOR: **POLYMER STABILIZED NEUROPEPTIDES**	

APPELLANT'S BRIEF ON APPEAL

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450
Mail Stop Appeal Brief - Patents

Sir:

This is an appeal to the Board of Patent Appeals and Interferences from the final Office Action mailed March 17, 2010, in the above-identified application in which pending claims 1-3, 6-16, 18, 19, 23, 24, 26, and 27 stand in final rejection.

The present paper is Appellant's Appeal Brief submitted in compliance with 37 C.F.R. § 41.37.

REAL PARTY IN INTEREST

The real party in interest is Nektar Therapeutics, the assignee of record of all right, title and interest in the present application.

RELATED APPEALS AND INTERFERENCES

No other prior or pending appeals, interferences or judicial proceedings are known to the Appellant, the Appellant's legal representative, or the Assignee, which may be related to, directly affect, or be directly affected by or have a bearing on, the Board's decision in the pending appeal.

STATUS OF CLAIMS

Claims 1-3, 6-16, 18, 19, 23, 24, 26, and 27 are pending, Claims 1-3, 6-16, 18, 19, 23, 26, and 27 and stand in final rejection and are the subject of this appeal. Claims 1-3, 6-16, 18, 19, 23, 24, 26, and 27 are presented in Appendix A.

Claims 4, 5, 17, 20-22, and 25 were previously canceled without prejudice.

Claim 24 is currently withdrawn as being directed to a non-elected specie.

STATUS OF AMENDMENTS

No amendments have been filed subsequent to the final rejection of the claims as summarized in the final Office action mailed March 17, 2010.

SUMMARY OF CLAIMED SUBJECT MATTER

The subject matter defined by the claims is directed to hydrophilic polymer-peptide conjugates of neuropharmaceutical peptide agents. The peptide portion of the conjugate is either the neuropharmaceutical peptide agent biphalin, or the neuropharmaceutical peptide agent [D-Pen^2, D-Pen^5] enkephalin ("DPDPE"). [*See* claim 1, appendix A.] The neuropharmaceutical peptide agent is linked to one or more water-soluble polymer chains, such as poly(ethylene glycol) or a copolymer of polyethylene glycol and polypropylene glycol, forming the polymer-peptide conjugate in a process generally known as "PEGylation" [at least in those instances where the polymer is a poly(ethylene glycol)]. [Specification at page 3, paragraph 26.] The hydrophilic polymer-peptide conjugate, when administered into the blood circulation of a mammal, is capable of transport across the blood-brain barrier ("BBB"). [Appellant's Specification at page 2, paragraph 12.] Thus, the polymer-peptide conjugate is able to effect a therapeutic result in the brain. [Claim 2, appendix A.]

Non-conjugated peptides typically fail to effectively cross the BBB. [Appellant's Specification at page 1, paragraph 8]. Such failure to cross the BBB severely limits the therapeutic effectiveness (or "efficacious effect") of such neuropharmaceutical peptide agents. However, Appellant has shown that a polymer-biphalin conjugate was able to pass through the BBB following administration, and has therapeutic effect (Figs. 1-6). [Appellant's Specification (Example 7) at page 8, paragraphs 94-115.] Additionally, Appellant has shown that the concentration of the polymer-DPDPE conjugate was significantly increased in the brain (Example 5) following its administration, rather than being trapped outside of the brain in its un-conjugated form. [Appellant's Specification at page 7, paragraph 77.]

The polymer conjugates of neuroactive peptide agents of the present claims are able to traverse the BBB, and overcome the problems associated with prior methods of brain delivery (*e.g.,* failure to effectively cross the BBB). [Appellant's Specification at page 1, paragraph 8.]

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The issues for review on appeal are:

1. Whether claims 1-3, 6-16, 18, 19, 23, 26, and 27 are obvious under 35 U.S.C. § 103(a) over the combination of Abbruscato, T.J., et al., (*J. Pharmacol Exp Ther.,* 1996; 276 (3): 1049-57, hereinafter "Abbruscato") and Delgado *et al.* (*Critical Reviews in Therapeutic Drug Carrier Systems*, 1992, vol. 9(3,4), 249-304, hereinafter "Delgado");

2. Whether claims 1-3, 6-16, 18, 19, 23, 26, and 27 are obvious under 35 U.S.C. § 103(a) in view of Ekwuribe, N., et al., International Patent Publication No. WO 01/19406[1].

Reconsideration of the above grounds of rejection is respectfully requested. The issue to be addressed is whether a polymer conjugate of a neuropharmaceutical peptide that is biphalin or DPDPE, where the peptide conjugate ***must*** cross the BBB (as recited in the claims), is rendered obvious by combined references that in no uncertain terms ***teach away*** from the subject matter embodied in the claims currently under consideration (discussed below). Appellant respectfully submits that the Examiner has failed to meet the requirements for establishing a *prima facie* case of obviousness.

[1] The summary of the issues for review on appeal is based upon the Appellant's understanding of the rejections summarized on page 3 of the final Office action dated March 17, 2010, in which the Examiner uses the term "or" in the third full paragraph appearing on the page. Appellant assumes that the term "or" with respect to the remarks which follow refers to the rejection of the claims in view of Ekwuribe alone rather in combination with Abbruscato. Should this not be the Examiner's intent, clarification of the rejection in writing is respectfully requested.

ARGUMENT

I. Rejection under 35 U.S.C. §103(a)

The pending claims stand rejected under 35 U.S.C. §103(a) as being unpatentable over the combination of Abbruscato and Delgado, or Ekwuribe. [Final Office Action mailed March 17, 2010, at page 3.] This is the only remaining rejection in this case.

The Examiner's grounds for this rejection, as well as Appellant's rebuttal thereto, are as follows.

A. The Claimed Invention

The claims under consideration are directed to hydrophilic polymer conjugates of the hydrophilic neuropharmaceutical peptide agents, biphalin or DPDPE. The polymer-peptide conjugates, as embodied in the sole independent claim (claim 1), consist of (i) a peptide that is either biphalin or DPDPE; (ii) covalently linked to one or more water-soluble polymer chains having a molecular weight from about 2,000 to about 100,000 daltons, and selected from either poly(ethylene glycol) or copolymers of ethylene glycol and propylene glycol; which (iii) when administered into the blood circulation of a mammal, is capable of ***transport across the BBB***. [Claim 1, appendix A (emphasis added.] Thus, the polymer conjugate is required to cross the BBB upon administration to the bloodstream.

Dependent claim 2 is directed to the feature of a conjugate as described above having an analgesic effect in the brain. [Claim 2, appendix A.]

Dependent claim 16 recites a pharmaceutical composition comprising the polymer-peptide neuropharmaceutical agent conjugate according to claim 1. [Claim 16, appendix A.]

Dependent claim 23 is directed to a conjugate as set forth above where the peptide is biphalin.

The remaining dependent claims recite features of a given polymer, or the particular position where the polymer is linked to the peptide (biphalin or DPDPE), and the like.

Delgado, when considered as a whole, at best teaches that the PEGylation of neuroactive ***proteins*** (*i.e.,* not peptides) improves certain pharmacokinetic ("PK") properties of the PEGylated protein. PK profiles include properties such as the amount of time the modified protein exists in the blood, or how fast the kidneys excrete the modified protein. [*See* Final Office Action mailed May 28, 2008, at page 4 citing Delgado.] While the Appellant is in agreement with the Examiner regarding the generally understood benefits of PEGylation as described by Delgado (*e.g.*, longer circulating half-life and reduced renal clearance, etc.), it is respectfully submitted that such improved PK properties are irrelevant to, and in no way predictive of, whether or not a compound will be capable of transport across the BBB.

Moreover, the Examiner has ignored the surprising and unexpected nature of the invention in light of other prior art, Abbruscato (among others), relied upon by Examiner. Abbruscato teaches that an increase in CNS entry of biphalin can be achieved by enhancing the drug's *lipophilicity* (See Abbruscato, Abstract, column 2). This is a clear ***teaching away*** from the Appellant's claims, in which rather than increasing the lipophilicity of either biphalin or DPDPE, the exact opposite is achieved. That is to say, the claimed conjugate, capable of passage across the BBB, possesses an enhanced *hydrophilicity* when compared to the unmodified parent molecule, not an enhanced lipophilicity. Such enhanced hydrophilicity is achieved by conjugation of hydrophilic polymers. This finding was ***unpredictable*** and ***surprising*** in view of the art of record.

Finally, a third piece of art currently relied upon by the Examiner is directed to modification of a hydrophobic drug such as etoposide by covalent attachment of a hydrophilic oligomer to achieve an amphiphilic prodrug (See Ekwuribe, entire document) for passage across the BBB. The nature of the drug itself prior to modification, the amphiphilic nature of the resulting prodrug, and the size of the oligomers employed, fail to even remotely suggest the subject matter encompassed by the pending claims.

The foregoing arguments are expanded in the sections which follow.

B. The Cited Art:

1. Abbruscato

Abbruscato, T.J., et al., (*J. Pharmacol Exp Ther.*, 1996; 276 (3): 1049-57, "Abbruscato". Abbruscato is a journal article describing the synthesis and blood-to-central nervous system pharmacokinetics and stability properties of halogenated biphalin derivatives, *p*-[Cl-Phe$^{4,4'}$]biphalin and *p*-[F-Phe$^{4,4'}$]biphalin. Abbruscato states that chlorohalogenation of biphalin was shown to improve CNS entry, most likely through an enhancement in *lipophilicity*...(Abstract). Further, Abbruscato summarizes the results of the study as suggesting that chlorohalogens at the para-phenyl$^{4,4'}$ position is a promising structural modification in the development of biphalin as a successful opioid drug for the clinic (Abstract, and page 1057, final sentence). Abbruscato further states that lipophilicity plays a critical role in the BBB penetration of certain peptides (page 1054, first column, final sentence of the first paragraph). This point is reiterated again at page 1056, first paragraph, lines 6 - 13. Finally, Abbruscato teaches that a decrease in BBB permeability observed for the fluorohalogenated derivative is correlated with a decrease in lipophilicity (*i.e.*, an increase in hydrophilicity).

As is evident from the remarks above, there is absolutely nothing in Abbruscato that would lead one of skill in the art to PEGylation of biphalin or DPDPE to provide a compound capable of transport across the BBB. Secondly, when viewed as a whole, the results described by Abbruscato lead to exactly the opposite conclusion - *i.e.*, that an increase in hydrophilicity of biphalin, such as that obtained via PEGylation, will lead to a compound having *diminished* transport across the BBB, as was reported for the fluorohalogenated biphalin derivative. Thus, not only does Abbruscato fail to suggest compounds of the type claimed by the Appellant, Abbruscato actually *teaches away* from compounds such as those encompassed by the claims. The Appellant's claimed compounds and the BBB transport property thereof are surprising and unexpected in

view of Abbruscato. Thus, there is absolutely nothing in the Abbruscato reference that would lead one of skill in the art to the Delgado reference, directed to PEGylated proteins. In fact, the teachings of Abbruscato would lead one of skill in the art *away* from the teachings of Delgado.

2. Delgado

Delgado *et al.* (*Critical Reviews in Therapeutic Drug Carrier Systems*, 1992, vol. 9(3,4), 249-304, "Delgado"). Delgado is a 1992 review article describing several PEGylated *proteins*, their pharmacological and chemical properties (antigenicity, renal clearance, bioactivity, etc.), methods of synthesis and analyses, and the like. Delgado fails to describe PEG-modification of small peptides such as biphalin and DPDPE. Nowhere does Delgado suggest a biphalin or DPDPE peptide-polymer conjugate, let alone that such a conjugate, or even a similar conjugate compound, may be capable of administration to the bloodstream and transport across the BBB, resulting in an analgesic effect. [*See generally* Delgado; *c.f.* Claims 1 and 2, appendix A]. Delgado is completely irrelevant to the patentability of the Appellant's claims, and in fact, has nothing to do with the transport of drugs across the BBB.

3. Ekwuribe

Ekwuribe, N., et al., International Patent Publication No. WO 01/19406 ("Ekwuribe"). The focus of Ekwuribe is *amphiphilic* prodrugs, rather than hydrophilic conjugates as recited in the Appellant's claims. Specifically, Ekwuribe describes the covalent modification of a *hydrophobic* drug (*e.g.*, etoposide, page 5, line 8) with an oligomer that can counteract the hydrophobic nature of the parent compound and improve its ability to penetrate the BBB (page 4, lines 14-16). More specifically, Ekwuribe describes amphiphilic prodrugs comprising a drug joined by a hydrolyzable bond to one or more PEG oligomers having 1 to 15 subunits (page 7, lines 27-29). Illustrative PEG oligomers are described structurally by formulae 1-10, and generally

possess a hydrophobic component (*e.g.*, $(CH_2)_n$ and $(CH_2)_p$)) and a hydrophilic component ($(OCH_2CH_4)_m$). Ekwuribe further characterizes the parent drug as *lipophilic* (page 4, line 17), and describes that conjugation to an oligomer as taught in that reference can improve the solubility of the drug in the bloodstream. Moreover, Ekwuribe states, "if the drug is hydrophilic, the PEG oligomer/polymer increases the lipophilicity and thereby improves the amphiphilicity of the prodrug" (page 11, lines 25-26). Consistent with Abbruscato, Ekwuribe teaches the exact opposite of the Appellant's claims - i.e., that for a hydrophilic drug (such as biphalin), one should modify the drug with a moiety that increases the lipophilicity of the resulting compound to improve its delivery across the BBB.

When viewed as a whole, it can be seen that Ekwuribe is focused on the problem of modifying lipophilic, small molecule drugs such as etoposide, by covalent attachment to a water-soluble oligomer such as PEG to enhance the drug's transport across the BBB. The point of Ekwuribe is to overcome the hydrophobicity of small molecules such as etoposide to thereby increase their hydrophilicity (page 5, lines 16-20) and to arrive at an *amphiphilic* compound.

Ekwuribe has nothing to do with hydrophilic, water-soluble peptide drugs such as biphalin and/or DPDPE, nor with the problem of improving transport of such hydrophilic peptides across the BBB. In fact, the conjugates of Ekwuribe are amphiphilic in nature, not hydrophilic compounds such as those claimed by the Appellants. Moreover, the particular PEG oligomers provided by Ekwuribe are of a size significantly smaller than those recited in the Appellant's claims (1-25 PEG (CH_2CH_2O-) subunits as recited on page 7, lines 28-30, corresponding to a molecular weight range of 44-1100 daltons). Finally, in support of Appellant's numerous arguments over the course of the prosecution history[2], Ekwuribe states that hydrophilic molecules (of which biphalin and DPDPE are exemplary) typically require an *active transport system* to traverse the BBB (page 2, lines 23-25), which is in contrast to the findings and claims of the Appellant. In fact, rather than

[2] See, e.g., Appellant's Amendment dated April 5, 2007, pages 9-12 with respect to the Wu reference; Appellant's Amendment dated February 15, 2008, pages 8-12 with respect to the Wu reference and the Delgado reference.

adopting Ekwuribe's guidance to rely on an active transport system to allow the hydrophilic molecules, biphalin and DPDPE, better cross the BBB, Applicants have shown molecules encompassed by the currently pending claims achieve better transport across the BBB through use of conjugation to poly(ethylene glycol) or a copolymer of polyethyleneglycol and polypropylene glycol.

In sum, there is nothing in any of the pieces of art relied upon by the Examiner, either when considered singly or in combination, that would lead one of skill in the art to the subject matter of the instant claims.

C. Examiner's Position

C. 1. It is the Examiner's position that it would have been obvious to one of ordinary skill in the art to PEGylate the neuropeptide, biphalin, in accordance with Delgado, in substitution for the chlorohalogenation taught by Abbruscato for the common purpose of increased stability of the peptide (final Office action, March 17, 2010, page 5, final paragraph to page 6, first paragraph). The Examiner has also further alleged, as a rationale, that "one would also expect an improvement of the PEGylated biphalin to cross the BBB given that stability was one of the contributing factors in the increased CNS uptake of biphalin as taught by Abbruscato, and PEGylation of proteins and peptides provides this property" (Final Office action, dated March 17, 2010, page 6, first paragraph).

C.2. The Examiner is further of the view that one would have been motivated to PEGylate biphalin because Ekwuribe teaches that PEGylating drugs adds an additional property of allowing the drug to be transported across the BBB. (Final Office action, page 6, first paragraph).

C.3. Finally, the Examiner has asserted (in complete disregard for the teachings of the art which have formed the basis for the current prosecution), that the effects recited in Appellant's claims 1 and 2 are to results which would necessarily follow upon

PEGylation of biphalin, *i.e.*, the ability to cross the BBB (Final Office action, page 6, final line of first paragraph).

Each of the Examiner's assertions as reiterated above is respectfully refuted, since the foregoing remarks clearly fail to consider the teachings of the prior art as a whole.

D. Appellant's Rebuttal

The issue is whether one skilled in the art, having the three cited references in hand, when considered along with knowledge commonly available to one of skill in the art, would have arrived at the Appellant's claimed invention. The Appellant respectfully submits that the answer to this question is "no", for the reasons that follow.

As reiterated by the Supreme Court in *KSR*, the framework for making an objective determination of obviousness is stated in *Graham*. [*KSR International Co. v. Teleflex, Inc.*, 82 USPQ2d 1385, 1391 (2007) *citing Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), *see also* M.P.E.P. § 2141.] Such an objective determination must include consideration of the claimed invention ***as a whole***, and also a consideration of the prior art references as a whole (***including disclosures that teach away from the claims***). [*Id.*] Appellant respectfully submits that the Examiner has failed to consider the invention as a whole, and overlooked portions of each of the disclosures that teach away from the instant claims.

The Examiner Failed to Establish a *Prima Facie* Case

The key to supporting any rejection under 35 U.S.C. § 103 is the clear articulation of the rationale for such a rejection. The Supreme Court has articulated, and this body has adopted, exemplary rationales supporting a conclusion of obviousness. [*See* M.P.E.P. §2141; *see also generally KSR* and the identified rationales supporting an obviousness rejection.] The Examiner has failed to clearly articulate a rationale supporting the obviousness rejections that finds support in the art relied upon, and

further considering the state of the art as a whole. The Examiner must consider whether one of ordinary skill in the art at the time of the invention would be prompted, with a reasonable expectation of success, to combine the alleged prior art elements, to achieve the compounds and features encompassed by and recited in the Appellant's claims. Or stated another way, "the operative question is thus 'whether the improvement is more than the predictable use of prior art elements....'" [*See* M.P.E.P. §2141, citing *KSR*.] Appellant maintains that the answer to the foregoing inquiries is "no" and "yes", respectively, for the reasons which follow.

Failure to Appreciate the Lack of Predictable Results

The prior art relied upon by the Examiner clearly indicates there was ***no*** expectation of success or predictable use of the prior art elements. As set forth in section I.B.1. above, Abbruscato states on numerous occasions that the improved CNS uptake characteristics of the chlorohalogenated biphalin derivative were likely due to its increased lipophilicity (Abbruscato, Abstract, page 1054, first column). Further to this point, Abbruscato states that a previous study had shown that lipophilicity plays a critical role in BBB penetration of certain peptides (page 1054, column 1, sentence at end of first paragraph). These findings are in direct contrast to the compounds recited in the Appellant's claims, which are hydrophilic in nature and incapable of effective levels of BBB transport. That is to say, based upon the teachings of Abbruscato, one skilled in the art would be led to increase the lipophilicity of biphalin or DPDPE to achieve improved BBB transport. The Appellant's claims are directed to just the opposite approach. Based upon this one feature alone, the Examiner has failed to establish a case of prima facie obviousness.

Combination of Prior Art Elements - No Rationale to Modify

Concerning the combination of Abbruscato and Delgado, in making the combination, the Examiner has alleged that one skilled in the art would substitute PEGylation for the chlorohalogenation taught by Abbruscato to achieve increased

stability of the peptide. The Examiner's assertion goes against the clear teachings of Abbruscato suggesting just the opposite, *i.e.*, increasing the lipophilicity of biphalin rather than increasing the hydrophilicity (*e.g.*, by covalent attachment of PEG) to achieve enhanced BBB transport. In light of the foregoing, a *prima facie* case of obviousness has not been made.

Failure to Consider the Claimed Invention as a Whole

The claimed invention, when considered as a whole, is directed to polymer conjugates of biphalin or DPDPE that must cross the BBB following introduction into the blood. In considering the Examiner's remarks, it appears that the Examiner has failed to appreciate that the Appellant's claimed modified biphalin and DPDPE neuropeptides must cross the BBB following administration into the blood of a mammal, and instead, has equated improved pharmacokinetics typically associated with PEGylation of proteins, such as increased plasma half-life and reduced proteolysis, with the expectation of transport across the BBB - which is in no way suggested by or in keeping with the cited art.

Failure to Consider the References as a Whole

Appellant submits that in characterizing the prior art references, the Examiner has failed to consider the teachings of these references as a whole, and has taken the teachings of these references out of context. The Examiner's failure to establish the obviousness of the claims over the combination of Abbruscato and Delgado is discussed in detail above.

With respect to Ekwuribe, the same argument holds. The Examiner has impermissibly simplified Ekwuribe to a "gist", alleging that one skilled in the art would have been motivated to PEGylate biphalin because Ekwuribe teaches that PEGylating drugs adds an additional property of allowing the drug to be transported across the BBB. The foregoing is an oversimplification of Ekwuribe, and not at all consistent with the actual teachings and suggestions of this reference when considered in its entirety. That

is to say, the Examiner's characterization of Ekwuribe fails to consider the teachings of the reference a whole. In no way does Ekwuribe lead one to the conclusion that PEGylation of drugs allows the drug to be transported across the BBB.

Rather, when viewed as a whole, it can be seen that Ekwuribe is focused on the problem of modifying lipophilic, small molecule drugs such as etoposide, by covalent attachment to a water-soluble oligomer such as PEG to enhance the drug's transport across the BBB. The point of Ekwuribe is to overcome the hydrophobicity of small molecules such as etoposide to thereby increase their hydrophilicity (page 5, lines 16-20) and form an amphiphilic compound capable of BBB transport.

Ekwuribe has nothing to do with hydrophilic, water-soluble peptide drugs such as biphalin and/or DPDPE, nor with the problem of improving transport of such hydrophilic peptides across the BBB. In fact, the conjugates of Ekwuribe are amphiphilic in nature, not hydrophilic compounds such as those claimed by the Appellants. Moreover, the particular PEG oligomers provided by Ekwuribe are of a size significantly smaller than those recited in the Appellant's claims [1-25 PEG (CH_2CH_2O-) subunits as recited on page 7, lines 28-30, which corresponds to a molecular weight range of 44 -1100 daltons]. In contrast, the Appellant's claims recite a polymer having a molecular weight of from about 2,000 to about 100,000 Daltons. Moreover, Ekwuribe states that hydrophilic molecules (such as biphalin and DPDPE) typically require an *active transport system* to traverse the BBB (page 2, lines 23-25), which is in contrast to the findings and claims recited of the Appellant.

In sum, there is nothing in Ekwuribe, or in any of the pieces of art relied upon by the Examiner, either when considered singly or in combination, that would lead one of skill in the art to modify biphalin or DPDPE to arrive at the subject matter of the instant claims.

Failure to Consider the State of the Art as a Whole

Although the Examiner has withdrawn two previously cited references from the current rejections of the claims relied upon in the final Office action, these two references further teach away from the Appellant's current claims and should be considered as further representing the state of the art at the time of the invention.

One such reference, Wu (Wu, D., and Pardridge, W.M., *Proc. Natl. Acad. Sci. USA*, **96,** 1999: 254-259), describes the modification of BDNF (a 27.0 kDa *protein*) via PEGylation to improve its PK properties, not to enable transport across the BBB. Specifically, Wu states that conjugation of the PEGylated BDNF protein to an OX26 MAb (the transport vector) *is required* to facilitate transport of the BDNF protein across the BBB (*See* Abstract). Wu stresses that for a neurofactor like the BDNF protein to have therapeutic utility, it is required that the protein be modified to both improve its plasma PK properties (the PEGylation step) and to enable transport across of the BBB (the coupling of the BDNF to a transport vector such as OX26 MAb step). Thus, Wu teaches that the therapeutic neurofactor protein BDNF must be conjugated to a transport vector to facilitate crossing of the BBB into the brain, and that PEGylation alone is insufficient for this purpose.

In a similar fashion, Sakane (Sakane, T., and Pardridge, W.M., *Pharmaceutical Research*, **14(8)**, 1997: 1085-1091) teaches that in order to impart the ability of the PEGylated BDNF protein to cross the BBB, the PEGylated BDNF must be further conjugated to a transport vector. Indeed, when considering the reference as a whole, Sakane demonstrates that BBB passage of the BDNF protein is *inhibited* upon PEGylation, and that BDNF protein *must be* coupled to a delivery system that enables BBB transport.

A more detailed account of the teachings of each of Wu and Sakane can be found in the following documents forming part of the prosecution history: Appellant's Amendment dated November 17, 2006, pages 7-9; Appellant's Amendment dated April

5, 2007, pages 9-12; Appellant's Amendment dated February 15, 2008, pages 8-12; Appellant's *first* Appeal Brief dated March 9, 2009, pages 10-17.

For the foregoing reasons, it is submitted that compounds having the features recited in the instant claims (PEGylated biphalin or DPDPE) and having the ability to cross the BBB, *e.g.*, to produce an analgesic effect, are surprising and unexpected in view of the art of record.

Nowhere has the Examiner identified any reason that would have prompted a person of ordinary skill in the art to modify or combine the disparate and contradictory elements of the art relied upon by the Examiner to arrive at the Appellant's claimed invention – a factor acknowledged by the Court in *KSR* (ibid) as relevant in a finding of obviousness. In view of the foregoing, in no way can the Appellant's claimed peptide conjugates as recited in claims 1-3, 6-16, 18, 19, 23, and 26-27 be considered to have been predictable to a person of ordinary skill in the art.

In addition to the foregoing arguments:

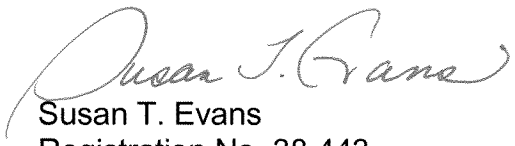
Regarding claim 3: Considering that Abbruscato explicitly teaches that increased lipophilicity is attributable to enhanced BBB transport of biphalin, claim 3, directed to a conjugate where the one or more water-soluble polymer chains is absent one or more lipophilic moieties, cannot be obvious in view thereof.

Appellant respectfully submits that there is clear deficiency in the *prima facie* case put forward by the Examiner. Appellant further respectfully submits that all of the pending claims are in condition for allowance and patentably define over the prior art. Withdrawal of the outstanding rejections under 35 U.S.C. §103(a), and a favorable decision on the allowability of the pending claims is requested.

Finally, the Examiner is reminded of the USPTO's commitment to the principles of compact prosecution - which seem to have been ignored in the application under consideration. The instant application has a filing date of August 25, 2003. Indeed, the Appellant's have provided arguments over at least the Wu reference since the reply to the first Office action dated November 17, 2006 through the Appellant's first Appeal Brief

filed March 9, 2009. It wasn't until consideration of the Appellant's first Appeal Brief that the Wu and Sakane references were withdrawn and prosecution reopened and two new references cited. (At this point, the case had already been pending before the Office for 6 years; it is unclear to the Appellant as to why these references were not earlier cited). These references (Abbruscato and Ekwuribe) are discussed herein. The Appellant has received a total of 6 Office actions in this case, and has made several earnest attempts via both amendment and argument to arrive at allowable subject matter. Appellant submits that there has been nothing "compact" about the prosecution in this application, and respectfully requests careful consideration of the remarks provided herein and a finding of patentability of the instant claims.

Respectfully submitted,



Susan T. Evans
Registration No. 38,443

Correspondence Address
Customer No.21968
Nektar Therapeutics
201 Industrial Road
San Carlos, CA 94070
Telephone: (650) 631-3100
Facsimile: (650) 620-6395

CLAIMS APPENDIX

1. A hydrophilic polymer-peptide conjugate consisting of a peptide that is either biphalin or [D-Pen^2, D-Pen^5) enkephalin (DPDPE) covalently linked to one or more water-soluble polymer chains having a molecular weight from about 2,000 to about 100,000 daltons and selected from either poly(ethylene glycol) or copolymers of ethylene glycol and propylene glycol, wherein said conjugate, when administered into the blood circulation of a mammal, is capable of transport across the blood brain barrier.

2. The conjugate of Claim 1, which, when administered to the blood circulation of a mammal, has an extended duration of analgesic effect when compared to the corresponding unconjugated peptide.

3. The conjugate of Claim 1, wherein said one or more water soluble polymer chains is absent one or more lipophilic moieties.

4 - 5. (Canceled).

6. The conjugate of Claim 1, wherein said peptide is covalently linked to at least one terminus of said one or more polymer chains.

7. The conjugate of Claim 1, wherein said peptide is covalently linked at an N-terminus to said one or more polymer chains.

8. The conjugate of Claim 1, wherein said water-soluble polymer chain is a copolymer of polyethylene glycol and polypropylene glycol.

9. The conjugate of Claim 1, wherein said water-soluble polymer chain is polyethylene glycol.

10. The conjugate of Claim 9, wherein said polyethylene glycol is selected from the group consisting of monomethoxypolyethylene glycol, branched polyethylene glycol, polyethylene glycol with degradable linkages in the backbone, homobifunctional polyethylene glycol, heterobifunctional polyethylene glycol, multi-arm polyethylene glycol, pendant polyethylene glycol, and forked polyethylene glycol.

11. The conjugate of Claim 1, wherein said peptide is conjugated to a single polyethylene glycol chain.

12. The conjugate of Claim 1, comprising biphalin covalently attached to two polyethylene glycol chains.

13. The conjugate of Claim 1 wherein said polymer chain is polyethylene glycol having a nominal average molecular weight of about 2,000 daltons to about 40,000 daltons.

14. The conjugate of Claim 13 wherein said polyethylene glycol has a nominal average molecular weight selected from the group consisting of 2000 daltons, 5000 daltons, 8,000 daltons, 10,000 daltons, 12,000 daltons and 20,000 daltons.

15. The conjugate of Claim 13 wherein said polyethylene glycol has a nominal average molecular weight of 2,000 daltons.

16. A pharmaceutical composition comprising a conjugate according to Claim 1 and a pharmaceutically acceptable carrier.

17. (Canceled).

18. The conjugate of Claim 9, wherein said polymer chain is linear.

19. The conjugate of Claim 1, wherein said peptide is covalently linked to said one or more water soluble polymer chains at a tyrosine residue of said peptide.

20 - 22. (Canceled).

23. The conjugate of Claim 1 wherein said peptide is biphalin.

24. (Withdrawn) The conjugate of Claim 1 wherein said peptide is DPDPE.

25. (Canceled).

26. The conjugate of claim 1, wherein said polymer chain is absent fatty acids and glycolipids.

27. The conjugate of Claim 1, wherein said polymer chain is monomethoxypolyethylene glycol.

EVIDENCE APPENDIX

None

RELATED PROCEEDINGS APPENDIX

None